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# Air Pollution and Mortality in Seven Million Adults: The Dutch Environmental Longitudinal Study (DUELS)

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**Short running head:** Air pollution and mortality in the Netherlands

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For the sensitivity analyses we used data collected by Community Health Services (GGD) of GGD Fryslan, GGD Gooi & Vechtstreek, GGD Hollands Midden, GGD Rotterdam-Rijnmond, GGD Zuid-Holland West, GGD Hart voor Brabant, GGD West Brabant, GGD Brabant Zuidoost, GGD Limburg Noord, GGD Zuid Limburg.

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## Abstract

**Background:** Long-term exposure to air pollution has been associated with mortality in urban cohort studies. Few studies have investigated this association in large scale population registries, including non-urban populations.

**Objectives:** The aim of the study was to evaluate the associations between long-term exposure to air pollution and non-accidental and cause-specific mortality in the Netherlands based on existing national databases.

**Methods:** We used existing Dutch national databases on mortality, individual characteristics, residence history, neighbourhood characteristics and national air pollution maps based on land used regression (LUR) techniques for particulates with an aerodynamic diameter less than 10 μm ($PM_{10}$) and nitrogen dioxide ($NO_2$). Using these databases, we established a cohort of 7.1 million individuals 30 years or older. We followed the cohort for seven years (2004 – 2011). We applied Cox proportional hazard models adjusting for potential individual and area-specific confounders.

**Results:** After adjustment for individual and area-specific confounders, for each 10 $\mu g/m^3$ increase, $PM_{10}$ and $NO_2$ were associated with non-accidental mortality [hazard ratio (HR) = 1.08; 95% CI: 1.07, 1.09 and HR = 1.03; 95% CI: 1.02, 1.03; respectively], respiratory mortality (HR = 1.13; 95% CI: 1.10, 1.17 and HR = 1.02; 95% CI: 1.01, 1.03; respectively), and lung cancer mortality (HR = 1.26; 95% CI: 1.21, 1.30 and HR = 1.10 95% CI: 1.09, 1.11; respectively). Furthermore, $PM_{10}$ was associated with circulatory disease mortality (HR = 1.06; 95% CI: 1.04; 1.08). but $NO_2$ was not (HR = 1.00; 95% CI: 0.99; 1.01). $PM_{10}$ associations were robust to adjustment for $NO_2$; $NO_2$ associations remained for non-accidental mortality and lung cancer mortality after adjustment for $PM_{10}$.

**Conclusions:** Long-term exposure to $PM_{10}$ and $NO_2$ was associated with non-accidental and cause-specific mortality in the Dutch population of 30 years and older.

## Introduction

Long-term exposure to air pollution has been associated with mortality in several cohort studies (Abbey et al. 1999; Beelen et al. 2014; Brunekreef et al. 2009; Carey et al. 2013; Cesaroni et al. 2013; Chen et al. 2013; Crouse et al. 2012; Dockery et al. 1993; Hales et al. 2012; Huss et al. 2010; Pope et al. 1995; Yap et al. 2012; Zeger et al. 2008). Although the evidence is increasing, heterogeneity in size of effect estimates between cohort studies has been identified (Hoek et al. 2013).

Cohort studies specifically designed for investigating individual risk factors are time consuming, labour intensive, often limited in size and relatively costly. To overcome these disadvantages recent studies have linked existing national databases of air pollution, non-accidentalmortality, individual characteristics, and residential history to assess the relationships between air pollution and mortality more efficiently (Beelen et al. 2014; Carey et al. 2013; Cesaroni et al. 2013; Chen et al. 2013; Crouse et al. 2012; Hales et al. 2012; Huss et al. 2010; Zeger et al. 2008). The aim of our study was to use existing national databases to evaluate the associations of long term exposure to air pollution [particulates with an aerodynamic diameter less than 10 µm ($PM_{10}$) and nitrogen dioxide ($NO_2$)] with non-accidental and cause-specific mortality in a cohort of 7.1 million Dutch residents.

## Methods

### The study cohort

In the Netherlands, population statistics are compiled by Statistics Netherlands (http://www.cbs.nl/en-GB/menu/home/default.htm) and are based on digital municipal population registers (Prins 2000). This registration system is known as the GBA (Gemeentelijke

Basis Administratie), the municipal basic registration of population data. The GBA was implemented on October 1, 1994.

Statistics Netherlands combines the data from the GBA into a longitudinal file for each individual registered in the GBA (de Bruin et al. 2004). These records start on January 1, 1995. Changes in demographic attributes (e.g. death, address, marital status, emigration) are updated yearly by adding additional information on the nature and the date of the change. In these files the individual identification number of the GBA is replaced by a meaningless, but unique identification number. This identification number is used to enrich the individual files with information from other central data sources maintained by Statistics Netherlands like the social statistical database which contains, among other, data from the tax authorities and about employment status (Arts and Hoogteijling 2002).

From the database with the longitudinal files of all Dutch inhabitants, we selected all individuals of 30 years or older on 1-1-2004, living at the same residential address since 1-1-1999. We used data about gender, age, marital status, and region of origin. The data about origin distinguishes between Dutch, western origin, and non-western origin. Individuals of non-western origin are those born in or with a parent born in Africa, Asia (except Japan and Indonesia, who are categorised as "western origin"), or Latin America. Given the relative large size of groups within non-western origin a distinction is made between Turkey, Morocco, and Surinam origin. Furthermore, we enriched the database with standardised disposable household income. This individual socio economic indicator is adjusted for differences in household size and composition.

We also used a socio economic indicator at 4-digit postcode level. These postcode areas comprise on average about 4,000 inhabitants. This social status indicator we used is derived every four years by The Netherlands Institute for Social Research, http://www.scp.nl/english/ (Knol 1998). Each postal code area receives a unique ranking for social status according to the income level, unemployment rate and education level of its inhabitants. The ranking is transformed to a 0-1 scale, with 1 being the lowest possible ranking on social status within the Netherlands. We took the indicator from 2002 and linked it to the cohort through the postcode of the residential addresses.

The follow up period of the cohort was from 1-1-2004 to 1-1-2011. Subjects were lost to follow-up if their final record in the longitudinal file ended before 1-1-2011 and death was not registered as a reason for termination. Emigration was the main cause of censoring.

The Dutch population registers are primarily intended for municipal administrative purposes. However, many national and non-governmental organisations benefit from them as well. Given the confidential character of the data, there is no free access to the population registers. Each organisation interested in receiving data on a regular basis, is given the opportunity to use the data upon a request to the Ministry for the Interior. The Ministry decides to which data the organization gets access.

All our analyses were performed within strict privacy rules, i.e. only researchers who received a signed permit were allowed to do analyses within a secured environment at our Institute. Prior to publication, Statistics Netherlands made sure that none of the analysis results showed potential reducibility to the individual level.

**Mortality outcomes**

A database with mortality data was available from Statistics Netherlands (Harteloh et al. 2010). We selected non-accidental mortality (ICD-10 codes A00-R99), circulatory disease mortality (ICD-10 codes I00-I99), respiratory disease mortality (ICD-10 codes J00-J99), and lung cancer mortality (ICD-10 codes C33-C34). A study of cause-of-death coding showed high reliability for these specific causes ( > 90% for major causes of death such as cancers and acute myocardial infarction and ca. 85% for respiratory disease mortality), (Harteloh et al. 2010).

**Air pollution exposure assessment**

We made use of previously published land use regression (LUR) models to produce high resolution air pollution maps (100 x 100 m grids) of annual mean concentrations of $PM_{10}$ and $NO_2$ in 2001. Details of development and validation of the LUR models are presented elsewhere (Vienneau et al. 2010). Briefly, for both pollutants regression models were derived from annual mean concentrations for the year 2001 based on routine measurement data from the Dutch national air quality monitoring network (http://www.rivm.nl/en/Documents_and_publications/Scientific/Reports/1999/maart/The_Dutch_National_Air_Quality_Monitoring_Network_monitoring_program_in_1999?sp=cml2bXE9ZmFsc2U7c2VhcmNoYmFzZT01OTAxMDtyaXZtcT1mYWxzZTs=&pagenr=5902). Predictor variables used for the modelling were traffic, land use, and topography integrated in a geographical information system. Addresses at baseline were linked to the estimated $PM_{10}$ and $NO_2$ concentration in the corresponding grid.

We did not assign $PM_{2.5}$ concentrations to cohort addresses, because in 2001 $PM_{2.5}$ was not measured in the national monitoring network. Two monitoring studies (Cyrys et al. 2003;

Eeftens et al. 2012) showed that the spatial variation of $PM_{10}$ in the Netherlands is largely driven by $PM_{2.5}$ ($R^2$ = 0.76 and 0.72) with a median ratio between $PM_{2.5}$ and $PM_{10}$ of 0.66 that was stable over time from 2000 to 2009.

**Statistical analyses**

Statistical analyses were performed with SAS version 9.1 (SAS Institute Inc., Cary, NC). We applied age-stratified Cox-proportional hazards regression models to estimate the associations (hazard ratio, HR, and 95% confidence interval, 95% CI) between (cause-specific) mortality and long-term exposure to $PM_{10}$ or $NO_2$. We used one-year age strata. We analysed the data with 1) models adjusting for age and gender ('unadjusted' model), 2) models adjusted for age, gender, marital status, region of origin, and household income (individual confounder model), 3) the individual confounder models extended with a social economic status indicator of postcode areas (full model). In addition we 4) extended the full model with the second pollutant to analyse the robustness of the one pollutant estimate when adjusted for the second pollutant. Statistical significant was defined as p-values < 0.05.

We explored non-linearity in the relationships between $PM_{10}$ and $NO_2$ exposure and mortality with natural splines (2 degrees of freedom). We used the likelihood ratio test ($p<0.05$) to compare spline models with linear models. We analysed these models with R version 2.15.1 (R-Foundation, Vienna, Austria).

To assess the sensitivity of our relative risk estimates to missing individual lifestyle factor data, we assessed the association between our air pollution exposure estimates and life style factors in a separate survey of adults across the Netherlands. We obtained data from health surveys from Community Health Services (http://www.ggdghor.nl/english/) conducted in 2003 – 2005. We

included data from 11 Community Health Services with available information on self-reported 4 digit postal code, age, sex, marital status, level of education, region of origin, smoking, body mass index (BMI), alcohol consumption, and exercise. Criteria for alcohol consumption were defined by a national working group of experts for the purpose of the Community Health Services health surveys. We calculated the age and sex adjusted mean $PM_{10}$ and $NO_2$ concentrations at 4-digit postal code level for different categories of smoking (current smoker, former smoker, never smoker), BMI (<18.5; 18.5-25; 25-30, >30), alcohol consumption (different categories of compliance to 3 criteria for responsible alcohol use), and exercise (compliance to 30 minutes of moderate exercise per day on at least 5 days per week). Subsequently, we additionally adjusted for the individual and neighborhood confounders that were also included in the Cox proportional hazard regression models (i.e. marital status, region of origin, individual socio economic status (using level of education in place of standardized household income, which was not available) and social status. In addition to these regression analyses, we calculated the prevalence of the different variables under study for different categories (deciles) of $PM_{10}$ and $NO_2$ exposure.

Furthermore, in the full population we additionally adjusted for area-level smoking-related mortality estimated based upon observed lung cancer rates (Janssen and Spriensma 2012).

In addition we assessed effect modification by stratifying our analyses by sex, age (30-65 or >65 years), socialeconomic status (five categories) and degree of urbanisation (five categories). Results are graphically presented.

## Results

On 1-1-2004 the total population of the Netherlands was 16,260,465, of which 9,936,994 had not moved in the previous five years (61%). Of these, 7,218,363 were of age 30 years or older (73%) and entered the cohort. Table 1 shows the characteristics of the cohort members on 1-1-2004. During the follow-up period until 1-1-2011 668,206 (9.3%) cohort members died from natural causes. Of these, 209,940 (31.4%) died from diseases of the circulatory system, 65,132 (9.7%) died from diseases of the respiratory system, and 53,735 (8.0%) died from lung cancer (Table 1).

Figure 1 shows maps of the distributions of the estimated $PM_{10}$ and $NO_2$ concentrations in the Netherlands for the year 2001. For the addresses of the cohort members the median $PM_{10}$ concentration was 29 $\mu g/m^3$ ($5^{th}$ – $95^{th}$ percentile: 24 $\mu g/m^3$ – 32 $\mu g/m^3$) IQR of 2.4; the median $NO_2$ concentration was 31 $\mu g/m^3$ ($5^{th}$ – $95^{th}$ percentile : 19 $\mu g/m^3$ – 44 $\mu g/m^3$), IQR = 10.0 $\mu g/m^3$. We estimated HRs per 10 $\mu g/m^3$ increase in the pollutant concentration. When expressed per Inter Quartile Range (IQR) the estimates for $PM_{10}$ will become smaller because the IQR for PM10 is smaller than for $NO_2$ . The range (and IQR) in $NO_2$ concentrations is larger than the range in $PM_{10}$ concentrations, as $NO_2$ is more influenced by local (traffic) emissions than $PM_{10}$, which is more affected by long range transport.

The correlation between $PM_{10}$ and $NO_2$ was 0.58.

The results of the Cox proportional hazard analyses are presented in Tables 2 ($PM_{10}$) and 3 ($NO_2$). The highest HRs were found for both pollutants and for each category of cause of death for the 'unadjusted' model. Adding individual confounders and area level for socio economic status reduced the magnitude of the associations.

We estimated the following associations for a 10-μg/m$^3$ increase in exposure to $PM_{10}$ and $NO_2$, respectively, based on the full models: for non-accidental mortality, HR = 1.08 (95% CI: 1.07, 1.09) and HR = 1.03 (95% CI: 1.02, 1.03); for mortality from respiratory diseases, HR = 1.13 (95% CI: 1.10, 1.17) and HR = 1.02 (95% CI: 1.01, 1.03) and for lung cancer mortality, HR = 1.26 (95% CI: 1.21, 1.30) and HR = 1.10 (95% CI: 1.09, 1.11). Only $PM_{10}$ was associated with circulatory disease mortality, (HR = 1.06; 95% CI: 1.04, 1.08 compared with HR = 1.00; 95%: 0.99, 1.01 for $NO_2$). For both pollutants, associations were strongest for lung cancer mortality ($PM_{10}$ HR = 1.26; 95% CI: 1.21, 1.30; $NO_2$ HR = 1.10; 95% CI: 1.09, 1.11).

In the two-pollutant models, HRs for $PM_{10}$ decreased for non-accidental mortality and lung cancer mortality, and increased for circulatory or respiratory disease mortality, still remaining statistically significant (Table 2). All HRs for $NO_2$ decreased after adjustment for $PM_{10}$, and the association with respiratory diseases was negative and no longer significant (Table 3).

To compare with previous cohort studies, we calculated HRs for $PM_{2.5}$ assuming that the association with $PM_{10}$ is driven by the $PM_{2.5}$ fraction (Beelen et al. 2014; Hoek et al. 2013). Based on a $PM_{2.5}/PM_{10}$ ratio of 0.66 (Cyrys et al. 2003; Eeftens et al. 2012) and $PM_{10}$ HRs from the fully adjusted model, we estimated the following for eacht 10 μg/m$^3$ increase in $PM_{2.5}$: for non-accidental mortality, HR = 1.13 95% CI: 1.11, 1.14), for circulatory disease mortality HR = 1.09 95% CI: 1.06, 1.12), for respiratory disease mortality HR = 1.18 95% CI: 1.15, 1.27) and for lung cancer mortality HR = 1.41 95% CI: 1.34, 1.49).

Associations between $PM_{10}$ and non-accidental, circulatory disease and lung cancer mortality did not deviate significantly ($p<0.01$) from linear (Figure 2). The association with respiratory disease mortality increased up to about 40 μg/m$^3$ and then unexpectedly decreased. Associations

between $NO_2$ and mortality only deviated significantly from linear for circulatory disease, for which no linear association was found (Table 3).

In addition to our main analysis, we conducted a separate analysis of associations of $PM_{10}$ and $NO_2$ with potential individual- and group-level confounders that were not available for the nation-wide study sample, since the presence or absence of associations would help clarify the likelihood of confounding by these characteristics. After excluding data from adults under the age of 30, information on life style factors from 63,796 subjects was available, from 1517 out of the 3985 four digit postal code areas across the Netherlands. Age and sex adjusted mean $PM_{10}$ and $NO_2$ for different categories of selected socio demographic characteristics and life style factors are presented in the Supplemental Material (Table S1 and Table S2 respectively). $PM_{10}$ concentrations differed statistically significant between the various categories, although these differences were small (<0.2 $\mu g/m^3$). After additional adjustment for marital status, region of origin, level of education and neighborhood social status, these differences decreased to 0.07 $\mu g/m^3$ for smoking and 0.10 $\mu g/m^3$ for BMI and 95% confidence intervals overlapped (Table S3). For $NO_2$, these differences in age and sex adjusted mean concentrations were somewhat larger: 0.64 $\mu g/m^3$ for current smokers compared to never smokers and 0.80 for BMI>30 compared to 18.5<BMI<25. After additional adjustment for marital status, region of origin, level of education and neighborhood social status, these differences decreased to 0.46 $\mu g/m^3$ both for smoking and for BMI, but remained statistically significant (Table S3). When evaluating differences in prevalence of life style and socio demographic characteristics across different categories (deciles) of $PM_{10}$ and $NO_2$ exposure, the percentage of current smokers and participants with BMI>30 are highest in the highest two deciles of $PM_{10}$ and $NO_2$ exposure. However, the percentage of non-Dutch nationality, low education, and average neighborhood

social status score follow a similar pattern, with the exception of non-Dutch nationality in the highest decile of $PM_{10}$ (Table S4).

Additional adjustment for smoking-attributable mortality reduced the HR for $PM_{10}$ by about 30% for non-accidental mortality (from 1.081 to 1.058) to 40% for the cause-specific mortalities (Table S5). The HRs for $NO_2$ changed marginally for non-accidental mortality from (1.027 to 1.022), for deaths from diseases of the circulatory system (non-significant), and for lung cancer mortality (from 1.097 to 1.083). The $NO_2$ HR for respiratory mortality changed from 1.015 to a non-significant 1.003.

In Figure 3 we present the HR's for nonaccidental, circulatory mortality, respiratory and lungcancer mortality per 10 ug/m3 $PM_{10}$ and $NO_2$ by sex, age, social economic status and degree of urbanisation. We did not find consistent patterns of effect modification across the different outcomes, although, with the exception of circulatory mortality, HRs tended to be closer to unity among those >65 years of age compared with younger residents.. For lung cancer, women were at higher risks for both, $PM_{10}$ and $NO_2$ exposure.

## Discussion

In this large Dutch nation-wide population cohort of over 7 million adults we observed positive significant associations between estimated long-term exposure to air pollution ($PM_{10}$ and $NO_2$) at the home address and non-accidental, circulatory disease, respiratory disease, and lung cancer mortality. We used large national demographic and geographical databases to assess these associations. Our results suggest that $PM_{10}$ is more consistently associated with mortality than $NO_2$.

The large size of the cohort allowed us to assess the small relative risks of ambient air pollution with more precision than typical individual cohort studies. Interestingly, we found highly significant associations between $PM_{10}$ and respiratory mortality. Associations between long-term exposure to fine particles and respiratory mortality have been inconsistent in previous individual cohort studies, partly due to a relatively small number of cases (Hoek et al. 2013). Our findings are in agreement with time series studies based upon registries that have shown consistent associations between day to day variation in air pollution and respiratory mortality. Consistent with the time series studies, our estimates for respiratory mortality are larger than for non-accidental mortality.

Another interesting finding is that though circulatory disease mortality was significantly associated with $PM_{10,}$ hazard ratios were smaller than for non-accidental mortality. Overall, in previous cohort studies Hazard ratios were larger for circulatory disease mortality, though with considerable variation between studies.(Hoek et al. 2013) We speculate that better medication has reduced cardiovascular mortality, complicating assessment of associations with risk factors including air pollution.

Recently, several studies were published that were based on national demographic databases linked to air pollution data (Carey et al. 2013; Cesaroni et al. 2013; Chen et al. 2013; Crouse et al. 2012; Hales et al. 2012; Huss et al. 2010; Zeger et al. 2008). In three systematic reviews on the health effects of long term exposure to air pollution (Brook et al. 2010; Chen et al. 2008; Hoek et al. 2013) an extensive overview is given of the published literature on mortality and long term exposure to air pollution. In the Supplemental Material Table S6 we summarize the results

of the national registry studies and recent papers on mortality outcomes from a large European study on air pollution and health. For comparisons we added our result into the table.

In our study we found particulate matter to be associated with all outcome measures that we have analysed. Our relative risk estimate for $PM_{10}$ on total mortality is higher than the relative risk estimate from a recent published study based on 19 European cohorts (Beelen et al. 2014) . Only 2 other registry based studies assessed the associations between mortality and $PM_{10}$(Carey et al. 2013; Hales et al. 2012). Both studies, like ours, reported higher HR for respiratory mortality than for cardiovascular mortality (although the Hales study included lungcancer mortality). A Dutch study of Beelen et al. (2008) also estimated higher HR's for respiratory mortality than for cardiovascular mortality (for $PM_{2.5}$), while Cesaroni et al. (2013) in Rome reported higher HR for $PM_{2.5}$ for cardiovascular mortality than for respiratory mortality. For $NO_2$ we found statistically significant associations with all outcomes except for circulatory disease mortality, which is in line with earlier Dutch cohort study results (Beelen et al. 2008) in which a non-significant association for $NO_2$ was reported. Again, our estimate on total mortality is higher than the relative risk estimate from the recent published European study (Beelen et al. 2014).Our results for non-accidental mortality are comparable with the results from the registry studies by Carey and Cesaroni and the Dutch cohort study by Beelen. Cause-specific results show more heterogeneity between the different studies presented in Supplemental Material S6. In the analyses in which we adjusted associations with $NO_2$ for $PM_{10}$ concentrations, the association between $NO_2$ and respiratory mortality disappeared while the $PM_{10}$ effects remained. This suggests that mortality effects of particles are not exclusively explained by traffic, as was suggested in a recent European wide study as well (Beelen et al. 2014).

Our estimates for lung cancer mortality for $PM_{10}$ and $NO_2$ are higher than published recently in the national cohorts (Carey et al. 2013; Cesaroni et al. 2013; Hales et al. 2012; Huss et al. 2010), but comparable with the $PM_{10}$ estimate for lung cancer incidence in a recently published study on the relation between long term exposure to air pollution and lung cancer incidence in 14 European cohorts (Raaschou-Nielsen et al. 2013). Adjustment for $NO_2$ levels reduced the estimate [HR = 1.093 (95% CI: 1.044, 1.144)] while the estimate for $NO_2$ was [HR = 1.080 (95% CI: 1.065, 1.096)]. This suggests that $PM_{10}$ and $NO_2$ represent different characteristics of the air pollution mixture which act independently, which may be related to the source of the pollution variability. In the European study no association with $NO_2$ was reported (Raaschou-Nielsen et al. 2013).

We found a tendency for lower HR's in the older age category (65+). This is in line with the suggestion of effect modification by age in the Rome cohort (Cesaroni et al. 2013) and consistent with a previous study in Norway (Naess et al. 2007). In contrast with Cesaroni et al. (2013), we did not estimate stronger associations for men than women, and for lung cancer, associations with both exposures were significantly stronger for women than men. We did not find clear evidence of modification by socialeconomic status, which is in line with the findings in the Rome cohort.

Although in general studies of long-term effects of air pollution on mortality qualitatively show similar results, differences in the quantitative outcomes remain.

Our results contribute to the evidence linking long-term ambient air pollution exposure to increased non-accidental and cause-specific mortality. Our study has several strengths. The study size is very large and includes all Dutch citizens of 30 years and older in 2004, living at least for

five years at the 2004 address which improves the long-term exposure classification. We used address level for all cohort members, based on the annual mean $NO_2$ and $PM_{10}$ concentrations at a 100x100 m grid. Further, due to the relatively low correlation between the two air pollutant components (R=0.58) we were able to disentangle the relative importance of the two components when adjusting for each other. We had individual information about important predictors of mortality at both the individual and ecological levels.

Apart from the strengths, there are also limitations of our study. Exposures were estimated by a LUR model for the year 2001 and assigned to the follow up period 2004 – 2011. Although the exposure assignment precedes the follow up period, we are not sure that the 2001 annual average adequately represents a longer exposure window which is relevant for long term exposure. However there is evidence from the literature that spatial distribution of air pollution is stable over 10-years periods (Cesaroni et al. 2012; Eeftens et al. 2011; Gulliver et al. 2011). Still, people might have moved since 2004 to unknown addresses and therefore changed their exposure.

Because of the limited availability of individual life style factors we adjusted for individual and area-level SES, as in the American Cancer Society study, ACS (Krewski et al. 2009) and the European Study of Cohorts for Air Pollution Effects, ESCAPE (Beelen et al. 2014) study. The two confounders represent different ‘ contextual’ environments. Overadjustment is a possibility, but unlikely, because the correlation between the two covariates was low (-0.11).

No information on individual risk factors such as smoking, diet, alcohol use and obesity was available. We evaluated the possibility if uncontrolled confounding from life style factors may have biased our results using data from over 60,000 30-65 year old participants of health surveys

conducted in 2003-2005 by 11 Community Health Services. We do not have appropriate references to substantiate the representativeness of this sub-group in comparison to our national cohort, but as the regions were spread over the Netherlands and the goal of the surveys is to select random samples, we think that exposure ranges are well covered in the sub-group and comparable with the exposure range in the national cohort.

After adjustment for age, sex, marital status, region of origin, level of education and neighborhood social status score, mean $PM_{10}$ and $NO_2$ exposures were only 0.1 $\mu g/m^3$ ($PM_{10}$) and 0.5 $\mu g/m^3$ ($NO_2$) higher among current smokers compared to never smokers, and among participants with BMI>30 compared to 18.5 < BMI<25. When looking at the prevalence of life style and socio demographic characteristics across different categories (deciles), we found that these differences were likely driven by a higher percentage of current smokers and participants with high (>30) BMI in the highest two deciles of $PM_{10}$ and $NO_2$ exposure.

As we observe associations for the whole exposure distribution we think it is unlikely that uncontrolled confounding from smoking or BMI has substantially biased our results (Figure 2 and Supplemental Material, Tables S1-S4.)

In a second sensitivity analyses we used regional age-standardised smoking attributable mortality fractions, 22-30% for men and 7-14% for women, in 40 NUTS-3 regions (Janssen and Spriensma 2012). The average population in these regions is about 400,000. We found that additional adjustment in the analyses with an area-level proxy for smoking reduces the HRs but did not materially affect the conclusions of the study (Supplemental Material, Table S5). There are several cohorts studies published with missing data on, presumably important individual confounders (Supplemental Material, Table S6), but most of them showed that relative risk

estimates did not materially change when some additional adjustment was made by using proxies for individual risk factors on an aggregated level (Cesaroni et al. 2013; Chen et al. 2013; Villeneuve et al. 2011; Zeger et al. 2008). In general, this suggests that there is evidence that the lack of individual data on smoking and BMI did not bias the results in such a way that conclusions drawn on data with missing information for some individual potential confounders are materially wrong. Krewski et al. showed that adjusting for self-reported smoking had little effects on the relative risk estimates in two different US cohorts (Krewski et al. 2005a; Krewski et al. 2005b). In the National English Cohort (Carey et al. 2013) the effect estimates were robust to adjustment for individual smoking and BMI (collected from individual patient cohorts).This was also acknowledged by Hoek et al. (Hoek et al. 2013) who concluded that effect estimates from the three large population cohorts without individual smoking data (Cesaroni et al. 2013; Crouse et al. 2012; Zeger et al. 2008) were not higher than those from the individual cohort studies.

## Conclusions

Long-term exposure to particulate air pollution ($PM_{10}$) and $NO_2$ was associated with non-accidental mortality, mortality from respiratory diseases, and lung cancer mortality in our study population of 7 million adults. Furthermore, $PM_{10}$ was associated with cardiovascular mortality. Associations with $PM_{10}$ were robust to adjustment for $NO_2$, and associations of $NO_2$ with non-accidental and lung cancer mortality remained after adjustment for $PM_{10}$.

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**Table 1.** Characteristics of the cohort (N=7,218,363) at baseline (2004

| Characteristic | Category | Number | (%) |
|---|---|---|---|
| Sex | male | 3,444,166 | 47.7 |
| Age | 30-40 | 1,053,506 | 14.6 |
| | 40-50 | 1,765,274 | 24.5 |
| | 50-60 | 1,804,214 | 25.0 |
| | 60-70 | 1,256,075 | 17.4 |
| | 70-80 | 877,444 | 12.2 |
| | 80 + | 461,850 | 6.4 |
| Marital status | married | 4,977,475 | 69.0 |
| | single | 924,165 | 12.8 |
| | widowed | 639,451 | 8.9 |
| | divorced | 528,753 | 7.3 |
| | other | 148,519 | 2.1 |
| Origin[a] | Morocco | 67,444 | 0.9 |
| | Turkey | 84,773 | 1.2 |
| | Suriname | 91,588 | 1.3 |
| | Non-western | 119,538 | 1.7 |
| | Western | 638,103 | 8.8 |
| | Dutch | 6,216,917 | 86.1 |
| Mortality | ICD-10 code | | |
| Total excl. ext. causes | A00-R99 | 668,206 | 9.3 |
| Disease of the circulatory system | I00-I99 | 209,940 | 2.9 |
| Diseases of the respiratory system | J00-J99 | 65,132 | 0.9 |
| Lung cancer | C33-C34 | 53,735 | 0.7 |

[a]Individuals of non-western origin are those born in or with a parent born in Africa, Asia (except Japan and Indonesia, who are categorised as " western origin"), or Latin America. Given the relative large size of groups within non-western origin a distinction is made between Turkey, Morocco, and Surinam origin.

**Table 2.** Hazard ratio's (95% CI) per 10 μg/m$^3$ increase in $PM_{10}$ levels at the home address in 2001 for non-accidental mortality, mortality from circulatory diseases, mortality from respiratory diseases and lung cancer mortality.

| $PM_{10}$ | Non-accidental HR (95% CI) | Circulatory diseases HR (95% CI) | Respiratory diseases HR (95% CI) | Lung cancer HR (95% CI) |
|---|---|---|---|---|
| Unadjusted model | 1.13 (1.12, 1.14) | 1.11 (1.09, 1.13) | 1.18 (1.14, 1.22) | 1.30 (1.25, 1.35) |
| Individual confounders model | 1.10 (1.09, 1.11) | 1.08 (1.06, 1.10) | 1.16 (1.12, 1.20) | 1.30 (1.25, 1.35) |
| Full model | 1.08 (1.07, 1.09) | 1.06 (1.04, 1.08) | 1.13 (1.10, 1.17) | 1.26 (1.21, 1.30) |
| Two pollutant model | 1.04 (1.03, 1.06) | 1.09 (1.07, 1.12) | 1.16 (1.11, 1.20) | 1.09 (1.04, 1.14) |

Unadjusted model: adjusted for age and gender.

Individual confounders model: adjusted for age, gender, marital status, region of origin, and standardized household income.

Full model: adjusted for neighborhood (postal digit) social status, in addition to the individual confounders.

Two-pollutant model: adjusted for estimated $NO_2/PM_{10}$ at the home address in 2001, in addition to the full model covariates.

**Table 3.** Hazard ratio's per 10 μg/$m^3$ increase in $NO_2$ levels at the home address in 2001 for non-accidental mortality, mortality from circulatory diseases, mortality from respiratory diseases and lung cancer mortality.

| $NO_2$ | Non-accidental HR (95% CI) | Circulatory diseases HR (95% CI) | Respiratory diseases HR (95% CI) | Lung cancer HR (95% CI) |
|---|---|---|---|---|
| Unadjusted model | 1.06 (1.06, 1.06) | 1.03 (1.03, 1.04) | 1.05 (1.04, 1.06) | 1.14 (1.13, 1.15) |
| Individual confounders model | 1.04 (1.04, 1.04) | 1.01 (1.01, 1.02) | 1.03 (1.02, 1.04) | 1.12 (1.11, 1.14) |
| Full model | 1.03 (1.02, 1.03) | 1.00 (0.99, 1.01) | 1.02 (1.01, 1.03) | 1.10 (1.09, 1.11) |
| Two pollutant model | 1.02 (1.02, 1.02) | 0.98 (0.98, 0.99) | 0.99 (0.98, 1.00) | 1.08 (1.07, 1.10) |

Unadjusted model: adjusted for age and gender.

Individual confounders model: adjusted for age, gender, marital status, region of origin, and standardized household income.

Full model: adjusted for neighborhood (postal digit) social status, in addition to the individual confounders.

Two-pollutant model: adjusted for estimated $NO_2$/$PM_{10}$ at the home address in 2001, in addition to the full model covariates.

## Figure Legends

**Figure 1.** Maps of the distributions of the estimated $PM_{10}$ and $NO_2$ concentrations in the Netherlands for the year 2001 (modelled with Land Use Regression models).

**Figure 2.** Estimated concentration–response curves (solid lines) and 95% CIs (dashed lines) for non-accidental mortality, circulatory disease mortality, respiratory disease mortality and lung cancer mortality for $NO_2$ and $PM_{10}$. Model adjusted for age, gender, marital status, region of origin and household income;

**Figure 3.** Adjusted HR (95% CIs) per 10 $\mu g/m^3$ increase in $PM_{10}$ (A) and $NO_2$ (B), by population characteristics and cause of death. Model adjusted for age, gender, marital status, region of origin, social economic status and household income; stratified as indicated on x-axis.

Social Economic Status categories based om the quintiles of the social status rankings; Urbanization based on addressdensity: (low: < 500 addresses/$km^2$; moderate low: 500 – 1000 addresses/$km^2$, medium: 1000 – 1500 addresses/$km^2$, moderate high: 1500 – 2500 addresses/$km^2$, high: > 2500 addresses/$km^2$).

Figure 1.

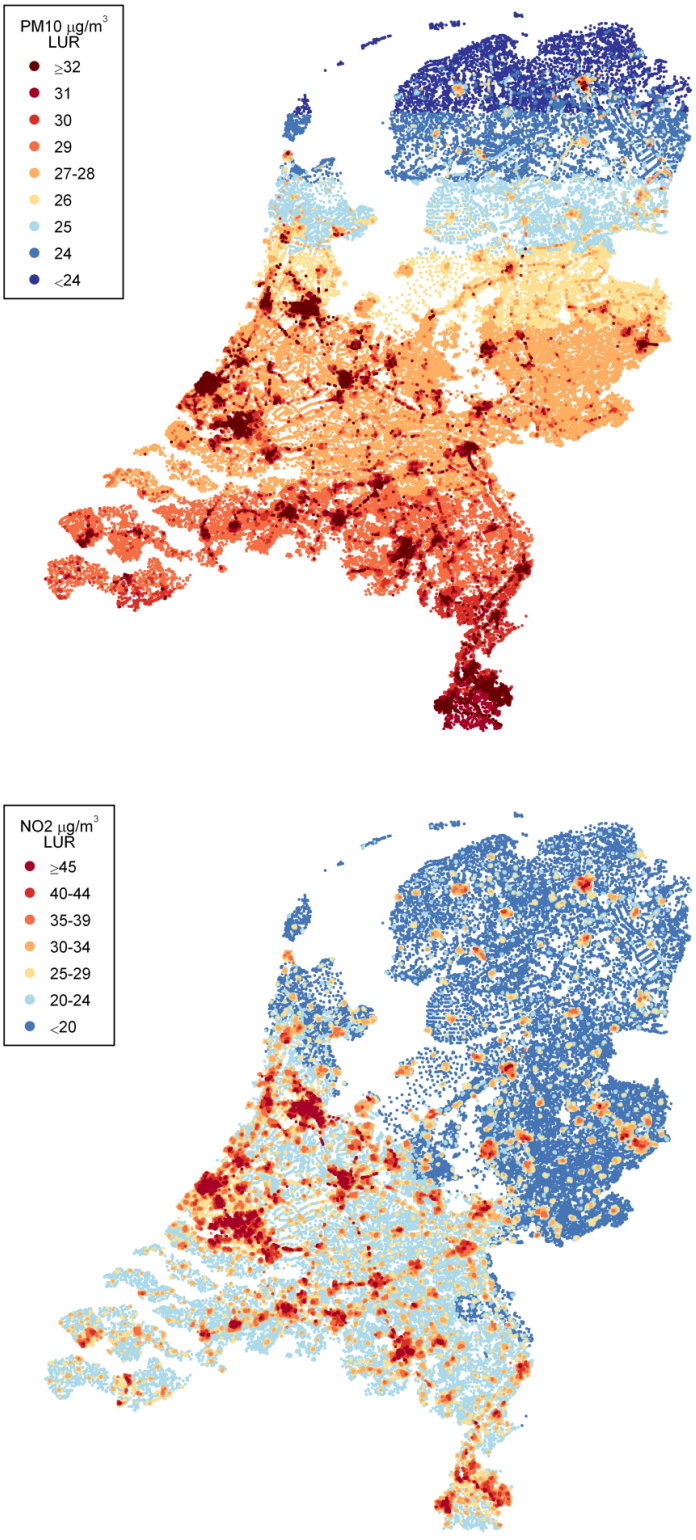

PM10 µg/m3
LUR
≥32
31
30
29
27-28
26
25
24
<24
NO2 µg/m3
LUR
≥45
40-44
35-39
30-34
25-29
20-24
<20

Figure 2.

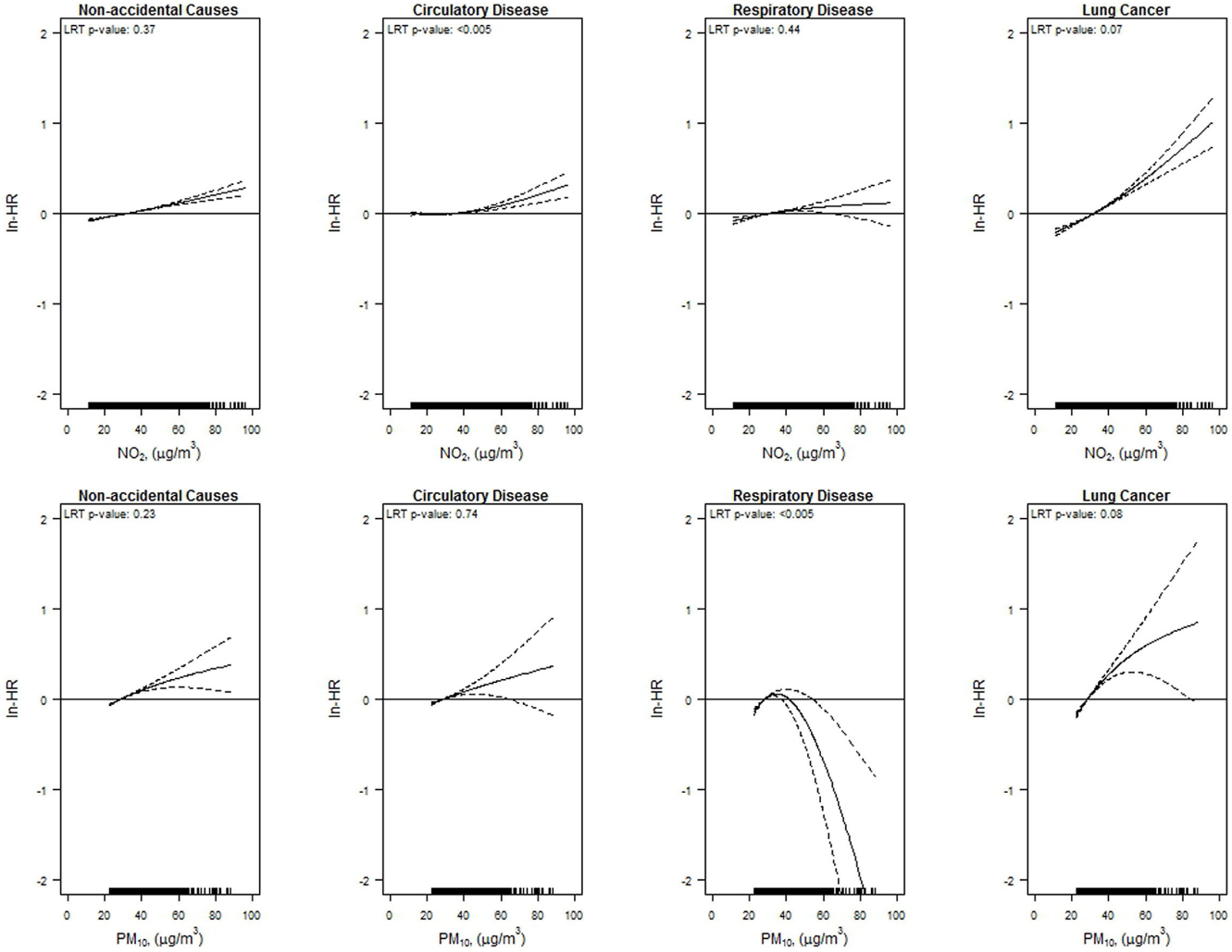
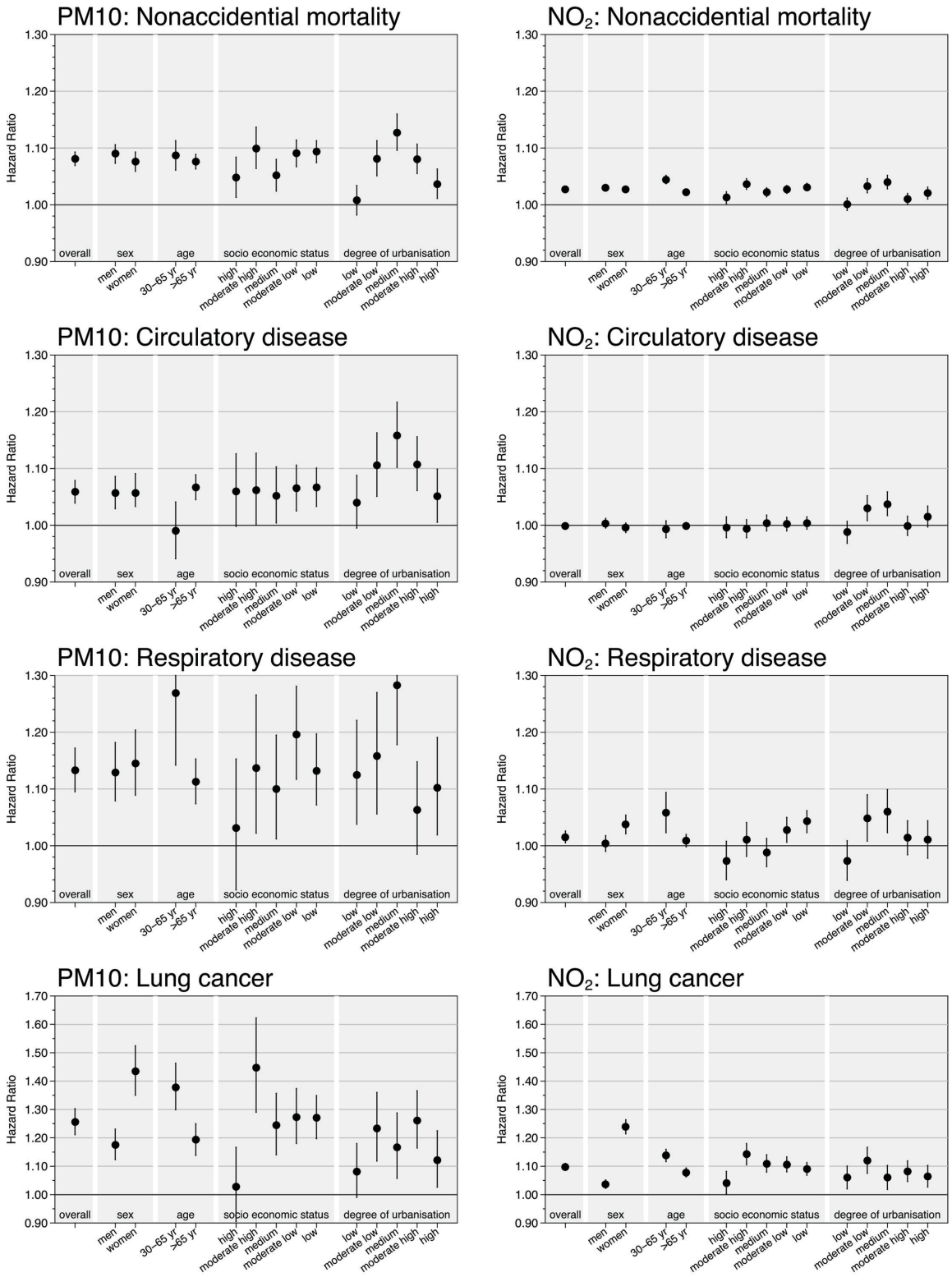

Non-accidental Causes
LRT p-value: 0.37
Circulatory Disease
LRT p-value: <0.005
Respiratory Disease
LRT p-value: 0.44
Lung Cancer
LRT p-value: 0.07
Non-accidental Causes
LRT p-value: 0.23
Circulatory Disease
LRT p-value: 0.74
Respiratory Disease
LRT p-value: <0.005
Lung Cancer
LRT p-value: 0.08
ln-HR
NO2, (µg/m3)
PM10, (µg/m3)

Figure 3.


PM10: Nonaccidental mortality
NO2: Nonaccidental mortality
PM10: Circulatory disease
NO2: Circulatory disease
PM10: Respiratory disease
NO2: Respiratory disease
PM10: Lung cancer
NO2: Lung cancer
Hazard Ratio
overall
sex
men
women
age
30–65 yr
>65 yr
socio economic status
high
moderate high
medium
moderate low
low
degree of urbanisation
low
moderate low
medium
moderate high
high